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Study of the intramolecular Heck reaction: synthesis of the bicyclic core of corialstonidine

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ABSTRACT

The intramolecular Heck reaction has been examined for the preparation of the core bicyclic structure of corialstonidine. Initial attempts to cyclise a vinyl iodide moiety onto a cyclic allyl alcohol were complicated by various side reactions. However, the corresponding process performed under reductive conditions on a conjugated ketone, obtained from the cyclic allyl alcohol, afforded the desired bicyclo[3.2.1] derivative. This compound possesses the skeletal features of the carbocyclic fragment of corialstonidine and is suitable for further transformations aimed towards the synthesis of the natural product or its derivatives.

Introduction

Quinoline derived antiplasmodial agents play a prominent role in the fight against malaria.[1–7] Quinine (Fig. 1), which has been isolated from the bark of the cinchona tree, was the first compound of this class that has been effectively used to treat malaria caused by *Plasmodium falciparum*. Several additional synthetic quinoline derivatives have been developed in an attempt to eliminate the adverse effects associated with quinine based therapy (Fig. 1).[1]

These compounds are believed to act by inhibiting the formation of hemozoin from heme, a transformation that is performed by the malarial parasite to prevent heme toxicity.[8,9] However, recent studies suggest a more complex molecular pharmacology, even for closely related quinolines.[10]

In addition to quinine, there are several other quinoline derived natural products which possess antimalarial properties.[11–14] Corialstonidine (Scheme 1) was isolated from *Alstonia coriacea* and was shown to have moderate activity against *Plasmodium falciparum*.[13] We recently began work with the aim of developing a synthetic route towards this natural product, based around the retrosynthetic analysis outlined in Scheme 1. The key step for the synthesis of bicyclic ketone **1** was envisaged as an intramolecular Heck reaction onto a cyclic allyl alcohol, which would directly afford the target compound via a cyclisation/β-hydride elimination/tautomerisation cascade.[15] Some supportive preliminary results related to this approach, obtained by studying a model system, have been published by our laboratory.[16]

Results and discussion

Cyclisation precursor **8**, which represents a *N*-protected derivative of **2**, was prepared in several steps starting from crotonaldehyde (Scheme 2). Interestingly, triene **6** underwent highly chemoselective ring closing metathesis to furnish cyclopentene **7** in excellent yield, while further deprotection afforded the target compound, allyl alcohol **8**. Detailed structural assignment of **8** based on the NMR data was rendered difficult due to the presence of rotamers as a result of the restricted rotation around the carbamate C—N bond. In order to exclude this feature, and consequently facilitate structural analysis, we attempted to remove the carbamate protecting group by exposure of **8** to TBAF.[17]

Although transformation of the vinyl iodide into the alkyne functionality was unintentional, analysis of the NMR data undoubtedly established the structure of **9**, confirming the existence of **8** as a mixture of rotamers. Interestingly, the $^{1}H/^{13}C$ NMR and NOESY data suggested that **9** was produced solely as the cis stereoisomer. This may also reflect the stereochemistry of **8**, assuming that under the reaction conditions to form **9**, isomerisation did not take place. With allyl alcohol **8** in hand the stage was set to explore the cyclisation step via an intramolecular Heck reaction. Due to the proposed stereochemistry of this compound we were aware of potential problems associated with cyclisation. The cis-arrangement of **8**, upon intramolecular *endo* addition

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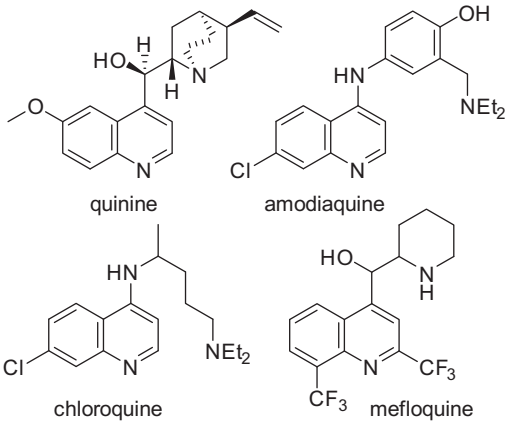
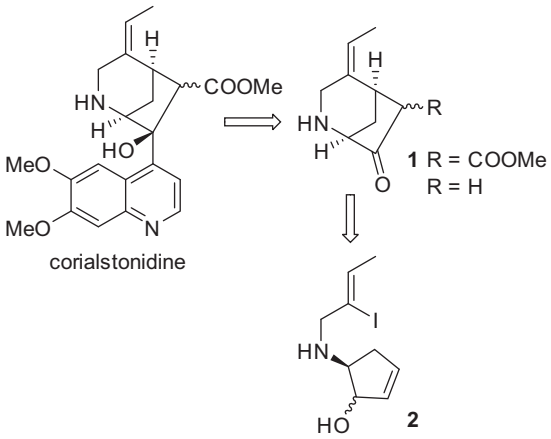
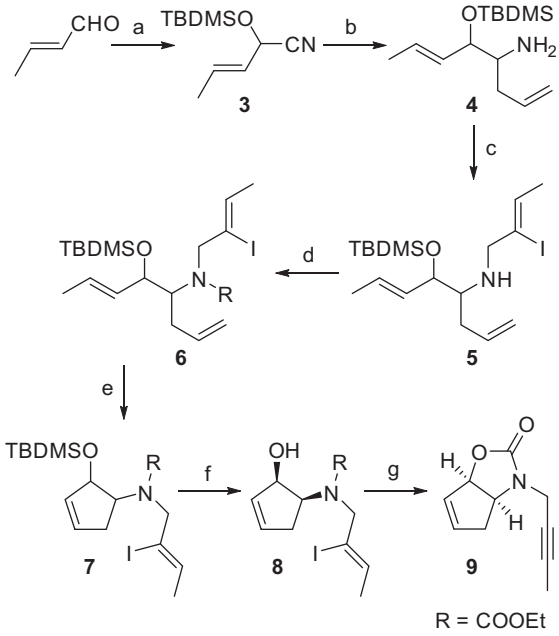


Figure 1. Examples of quinoline derived antimalarial drugs.



Scheme 1. Retrosynthetic plan.

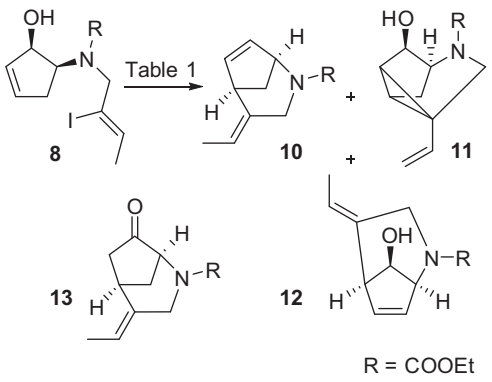


Scheme 2. Synthesis of cyclisation precursor **8**. Reaction conditions: (a) (i) KCN, AcOH, MeOH, 0 °C → r.t., 2 h (ii) TBDMSCl, imidazole, DMF, 0 °C → r.t., 16 h, 60%; (b) (i) allylMgBr, Et_2O, r.t., 1 h (ii) $NaBH_4$, MeOH, −78 °C → 0 °C, 2 h, 56%; (c) Z-1-bromo-2-iodo-2-butene, Cs_2CO_3, 4Å MS, THF/DMF, 90 °C, 16 h, 74%; (d) ClCOOEt, NaH, THF, −20 °C → r.t., 16 h, 86%; (e) Grubbs I (3 mol %), DCM, r.t. 16 h, 91%; (f) $PdCl_2(CH_3CN)_2$ (5 mol %), acetone/H_2O, 55 °C, 6 h, 77% (g) TBAF, THF, r.t., 1 h, 75%.

(related to the allyl alcohol functionality) of the vinyl palladium species onto the allyl moiety, would position the [Pd]I and OH substituents in a *syn* relationship. This stereochemical outcome would not favour *syn* Pd[H] elimination,[17,18] which would, after tautomerisation, lead to the desired ketone. Although *anti* Pd[H] elimination has been reported in the literature,[19,20] there remained an additional reaction pathway arising from the potential for *syn* Pd[OH] elimination.[21]

To explore the reactivity of **8**, the intramolecular Heck reaction was initially performed under standard conditions using Et_3N as the base in toluene (Scheme 3, Table 1).[22–25] The reaction afforded a separable mixture of three products (**10**–**12**) in a combined yield of 71%, while the desired bicyclic ketone **13** was not produced (Scheme 3). We also observed that the stereochemistry of the exocyclic double bond in the major component, compound **12**, was reversed compared to that of the same functional group in cyclisation precursor **8**. Performing the reaction under alternative conditions employing Ag_2CO_3 or Et_3N/K_3PO_4 with phenol as an additive resulted in a similar outcome (Table 1).[26]

Examination of the reaction pathway suggested that the transformations leading to **10**–**12** were initiated, as expected, by *endo* cyclisation (related to the allyl alcohol functionality) to generate intermediate **14** (Scheme 4). The *syn* elimination of [Pd]OH from compound **14** afforded **10** which further supported the stereochemical assignment of **8** that was proposed from the structural elucidation of **9**.[21,27–29] Only cis **8** would lead to the required cis [Pd]OH orientation for formation of **10** via [Pd]OH elimination. The alternative trans stereochemistry of **8** would result in a trans [Pd]OH relationship upon cyclisation, which would promote formation of the desired ketone **13** via a *syn*-[Pd]H elimination/tautomerisation cascade, however this was not observed. Intermediate **14** was also involved in the formation of compounds **11** and **12** (Scheme 4). 3-*Exo* cyclisation, involving the alkene moiety in **14**, giving **15**, followed by [Pd]H elimination yielded product **11**. Compound **12** was formed via a cycloreversion process from **15** which explains the stereochemistry of the newly formed exocyclic double bond.[26,30–32] Namely, cycloreversion leading to the

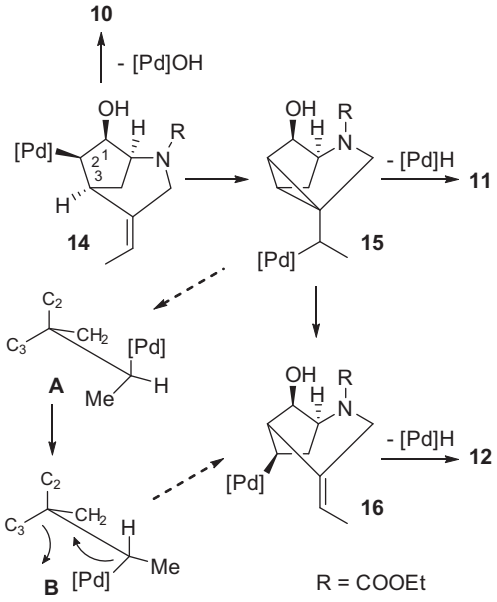


Scheme 3. Cyclisation reaction of allyl alcohol **8**.

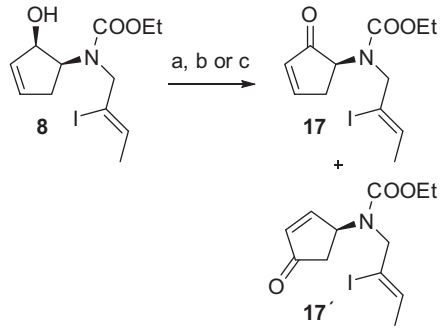
Table 1
Reaction conditions for the transformation of **8**

Entry	Base[a]	**10** (%)[b]	**11** (%)[b]	**12** (%)[b]
a	Et_3N	9	15	47
b	Ag_2CO_3	trace	trace	41
c	Et_3N/K_3PO_4/PhOH	10	10	55

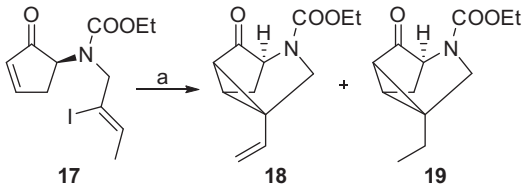
[a] Conditions: **8** (0.28 mmol), $Pd(OAc)_2$ (0.028 mmol), PPh_3 (0.056 mmol), toluene (29 mL), 110 °C, 16 h, base: Entry a, Et_3N (0.56 mmol); Entry b: Ag_2CO_3 (0.84 mmol); Entry c: Et_3N (1.68 mmol), K_3PO_4 (0.84 mmol), PhOH (0.056 mmol).
[b] Isolated yield after column chromatography.



Scheme 4. Rationalisation of the cyclisation reaction of **8**.

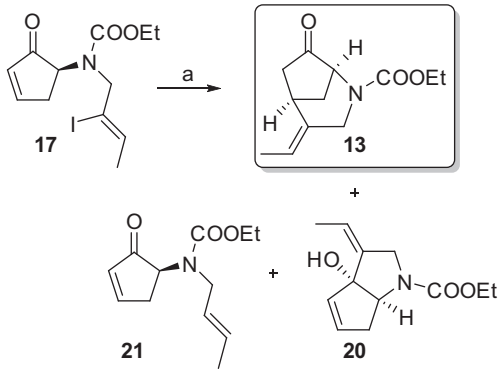


Scheme 5. Synthesis of conjugated ketone **18**. Reaction conditions: (a) DMP, CH_2Cl_2, r.t., 1 h, 74%, **17**; (b) PDC, CH_2Cl_2, r.t., 6 h, 82%, **17**/**17′** 15.4:1; (c) $(COCl)_2$, Et_3N, DMSO, −78 °C → r.t., 2 h, 70%, **17**/**17′** 1.3:1.



Scheme 6. Cyclisation reaction of conjugated ketone **17**. Reaction conditions: (a) $Pd(OAc)_2$ (10 mol %), PPh_3 (20 mol %), HCOONa, DMF, 120 °C, 18 h, 50%, **18**/**19** 1.7:1.

formation of a C(3)—[Pd] bond requires rotation around the C—C bond as illustrated by A → B (Scheme 4). This positions the C—[Pd] bond *syn* to the C—C_3 bond which is broken, altering the stereochemistry of the double bond. Although the reaction outlined in Scheme 3 proceeded via an initial *endo* cyclisation, as expected based on our model system study,[16] the desired bicyclic ketone **13** was not observed. At this point, instead of pursuing the same approach using trans **8**, which would have required an alternative synthetic route, we opted for the preparation of conjugated ketone **17** and an exploration of the intramolecular reductive Heck reaction.



Scheme 7. Synthesis of bicyclic ketone **13**. Reaction conditions: (a) $Pd(OAc)_2$ (10 mol %), PPh_3 (20 mol %), Et_3N, DMF, 120 °C, 18 h, **13** 30%, **20** 10%, **21** 15%.

Ketone **17** was accessible via oxidation of alcohol **8** with Dess–Martin periodinane (Scheme 5).[33,34] Interestingly, initial attempts to perform this transformation under Swern conditions[35] furnished a 1.3:1 mixture of **17** and **17′**. 1,3-transposition of allyl alcohols under oxidative conditions, which is reflected in the structure of ketone **17′**, has been observed with various reagents and has a synthetic significance.[36] In our case **17′**, was likely to be the result of a S_N2' process involving DMSO and the sulfonium intermediate generated from **8** followed by a base promoted elimination. Two products were also obtained using PDC which favoured the expected **17**.

Initial attempts to cyclise **17** under reductive Heck reaction conditions were disappointing, yielding an inseparable mixture of **18** and **19** in 50% yield (Scheme 6).[37–39] Clearly, after the initial carbopalladation, the 3-*exo* cyclisation (related to the **14** → **15** transformation, Scheme 4) was a favoured process over reduction of the intermediate, thus affording **18** and **19**.

Assuming that a low concentration of HCOONa in solution might be the reason for slow reduction of the initial intermediate, the same reaction was performed employing Et_3N as the reducing agent (Scheme 7).[40] Finally, the desired ketone **13** was isolated in 30% yield as well as two byproducts, **20** and **21**. Tertiary alcohol **20** was likely produced by nucleophilic addition of the vinyl-palladium species onto the ketone functionality, a process that is not typical for the mainly electrophilic organopalladium(II) species but which has been previously observed.[41–46] Product **21** results from reductive interception of the intermediate generated upon the initial oxidative addition of the palladium catalyst onto the vinyl iodide. Although this reaction requires further optimisation, these results suggest that the key bicyclic ketone in the proposed synthesis of corialstonidine can be accessed by the disclosed route.

Conclusions

Model studies using the intramolecular Heck reaction to assemble the skeleton of the bicyclic fragment of corialstonidine have led to the synthesis of the key ketone intermediate. This investigation has demonstrated the complexity of these Pd-catalysed processes and a fine interplay between the various steric and electronic factors which subtly control the reaction pathway. Our current work is focused on the enantioselective preparation of the ketone intermediate and completion of the synthesis.

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Supplementary data

Supplementary data (Experimental procedures and copies of the spectral data for selected compounds) associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2015.03.129

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